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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/011,855	12/04/2001	Russell Baumann	034827-0702	5245

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EXAMINER	
LI, BAO Q	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 10/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/011,855	BAUMANN ET AL.	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 8-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 8-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment filed on March 19, 2003 has been acknowledged. **First Applicants are reminded that the response has a typographic error in that the line 1 of the paragraph 2 on page 4 should be changed as claims 8-13 rather than claims 1-18.** Claims 2-7 have been canceled. Claims 1 and 8 have been amended. Claims 1 and 8-13 are pending.

Election/Restrictions

1. Applicant's election without traverse of Group III, claims 8-13 in Paper No. 9 is acknowledged. However, Applicants amend claim 8 to depend on claim 1 and asserted that claim 1, therefore belongs to group III, claims 1 and 8-13 should be rejoined and examined together.

2. Applicants' argument has been fully considered. Claims 1 and 8-13 are considered before the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1 and 8-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 1 is rejected because it fails to define which " an enzyme " is referred in the claim. The claim is interpreted in light of the specification; however, the limitation of the specification cannot read into the claim. Applicants' attention is directed to MPEP, which states: "The inquiry during examination is patentability of the invention as applicant regards it. If the claims do not particularly point out and distinctly claim that which applicants regard as their invention, the appropriate action by the examiner is to reject the claims under 35 U.S.C. 112, second paragraph. In re Zletz, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989). In the instant case, because there are so many enzyme that is able to cleave nucleic acid, if

applicants wish to claim a particular enzyme, please amend the claim to specify the intended enzyme.

5. Claim 9 recites the limitation "step (a)" in 8. There is insufficient antecedent basis for this limitation in the claim. This affects the dependent claim 10. Please amend claim to its correct dependency.

6. Claim 11 recites the limitation "test sample" in 8. There is insufficient antecedent basis for this limitation in the claim. Please amend claim to its correct dependency.

7. Claim 12 recites the limitation "nucleic acids" and step (a) in claim 8. There is insufficient antecedent basis for this limitation in the claim. Please amend claim to its correct dependency. This affects the dependent claim 13.

8. Claim 13 recites the limitation of the "lambda phage-HCV ribonucleic acid hybrids" in claim 2. There is insufficient antecedent basis for this limitation in the claim. Please amend claim to its correct dependency.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1, 8-10 and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kleiber et al. (J of Molecular. Diagnosis, 2000, Vol. 2, No. 3, pp. 158-166), Kawai et al. (Journal of Medical Virology 1999, Vol.58, pp. 121-126), Resnick et al. (US Patent No. 5,527,5669A), Michinori et al. (JP 103899-A/1), Scherer G. (Nucleic Acids Res. 1978, Vol. 5, pp. 3141-3156) and Lee et al. (US Patent NO. 6,316,610B2).

11. Claimed invention is drawn to a method of detecting hepatitis C virus (HCV) in a biological sample as listed in claim 11 by using a fluorescent probe-based PCR assay by employing 5'-3' nuclease to cleave the double fluorescent dyes labeled probe during the PCR,

which uses a pair of oligonucleotide primers having the sequence set forth in SEQ ID NO: 1 and SEQ ID NO: 2 that are all selected from the 5' untranslated conserved region, and a pair of probe, a target probe having the sequence set forth in SEQ ID NO: 3 conjugated with a reporter fluorescent dye VIC and a quencher dye TAMRA to detect the target HCV nucleic acid and an internal control probe having a sequence set forth of SEQ ID NO: 6 (lambda T7 RNA polymerase binding site) conjugated with reporter fluorescence dye FAM and quencher dye TAMRA to assessing the efficiency and accuracy of the assay system. The internal positive control HCV nucleotide is provided as a lambda phage-HCV ribonucleic acid hybrids that are introduced into the test sample prior to the isolation of nucleic acids from said sample and the testing nucleotide acids are purified prior to the PCR and amplification. The probes are hybridize with said amplified HCV nucleic acids in the presence of 5'→3' nuclease that cleaves said probe and generate a detectable signal indicating the presence or amount of HCV nucleic acids in the test sample.

12. Kleiber et al. explicitly teaches a fluorescent probe-based PCR method based on the TaqMan 5'-nuclease assay format that is used for detecting HCV. The test comprises (1) a test sample isolated from clinical specimens; (2) an pair of primers selected in a highly conserved 5" untranslated region of the HCV genome that are suitable for amplifying both target HCV nucleotide sequence and internal HCV positive control HCV nucleotide since the internal control (IC) of HCV is selected as an RNA transcript with primers region identical to those of the targeted HCV and an unique probe region; and two probes, one specific for the target HCV and one specific for an internal control. The ribonucleic acids (RNA) are first isolated from the serum or plasma from the patients infected with chronic HCV prior to the amplification and the internal control (IC) HCV RNA transcript is generated by transcribing HCV from a cloned HCV cDNA carried by a plasmid. Both RNA samples are added to each test sample before processing the amplification. The samples are fist amplified with primers and then the DNA replication is detected with dual-labeled HCV-specific and IC-specific dual, fluorescently labeled probe oligonucleotides. The probes contains a quencher and a fluorescent reporter, FAM is sued for the HCV-specific probe and HEX for the IC-specific probe. In the intact probe, the quencher absorbs fluorescence emitted by the reporter. The 5' nuclease activity of the polymerase degrades the hybridization probe during the replication, thereby releasing the reporter and producing an

increase in fluorescent emission. The disclosure of Kleiber et al. differs from the claimed invention in that they do not explicitly teach that the internal positive control is a lambda HCV hybrids and the primers have sequences set forth of SEQ ID NO: 1and SEQ ID NO: 2, an HCV specific probe has a sequence set forth SEQ ID NO: 3. Kleiber et al. do not teach to use lambda T-7 RNA polymerase promoter binding region of SEQ ID NO: 6 as a specific internal control probe (IC). Further, Kleiber et al. do not teach to use VIC as a reporter dye and TAMRA as a quencher dye for labeling the probes.

13. Kawai et al. discloses a similar method of TaqMan for detecting HCV. The method comprises IN HCV control that is an HCV RNA transcribed from pGEM3Zf(+) plasmid DNA by using T7 RNA polymerase (see section of preparation of control HCV RNA). Kawai et al. also teach the HCV specific probe is labeled with dual fluorophores of FAM at the 5' and TAMRA at the 3' (See lines 1-3 on 2nd paragraph of page 122).

14. Resnick et al. teach a pair of primers of SEQ ID NO: 4 and 18 that are used for detecting the presence of HCV RNA by PCR, which are 100% identical to the SEQ ID NO: 1 and 2. Resnick et al. particular teach this pair of primers, which are capable of detecting the presence of HCV genomic nucleic acid regardless of the strains because the primers hybridize to sequences from the 5' untranslated conserved regions of HCV genome and, therefore, they bind to a variety of strains (lines 34 on col. 3 through lines 1 to 14 on col. 4, and Table 1 and Table 2).

15. Michinori et al. disclose a probe of SEQ ID NO: 1 having 37 nuclei acids in that the nucleic acids residues 10-33 is 100% identity to the claimed probe of SEQ ID NO 3. The said probe is also used for detection of HCV RNA suitable for a fluorescence dye labeling (see line7 on page 10).

16. Regarding to the IC specific probe, because the specific sequence in the IC HCV positive control is derived from lambda phage DNA, the sequence of the full length of lambda phage DNA sequence is known in the art as evidenced by the disclosure of Scherer G (See entire document), and a selection of a sequence fragment comprising the sequence set for the of SEQ ID NO: 6 as an IC HCV positive control or any probe selected according to the disclosure of a full length lambda phage DNA sequence would be obvious for s person with ordinary skill in the art. Each sequence including the SEQ ID NO: 6 would work equally well unless applicants

particular provide an evidence that only SEQ ID NO: 6 works unexpected well over other selected probe within the range of the sequence disclosed by Scherer G.

17. Regarding to the VIC fluorescent dye, Lee et al. disclose method for using many fluorescent or quencher dye to able the probe oilgonucleotide, in which VIC and FAM are all suitable for labeling oligonucleotide probe through the 5' end of oligonucleotide (Claims 18 and 29).

18. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was filled to be motivated by the recited references and to combine methods taught by Kleiber et al., Kawai et al., Resnick et al., Michinori et al., and Lee et al. to established a method of detecting HCV RNA in a biological sample. Because the advantage of using TaqMan method with IC control in the testing sample and two probes with dual labeling fluorescent and quencher dyes are clearly demonstrated by Kleiber et al. To substitution of a pair of primers more suitable for detecting broad strains of HCV disclosed by Resnick et al and selection of a probe of SEQ ID NO: 1 as disclosed by Michinori et al. which is within the region amplified by the two primer and selection of a specific IC probe specific to the lambda phage T-7 polymerase promoter region operably linked to the targeted HCV sequence disclosed by Sherer G. should be obvious for a person with ordinary skill in the art because all the sequences are already known in the art. Especially, Kleiber et al. teach that the IC specific probe should be specific for the IC but not for the HCV. The enclosure of an IC in the TaqMan assay prevent the false negative results and also increase the throughput by eliminating the need of run external standards (See lines 7 to 22 on 1st col. of page 165). As there are no unexpected results have been provided, hence the claimed invention as a whole is prima facie obvious absence unexpected results.

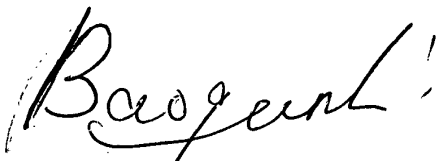
Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 7:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Bao Qun Li
October 09, 2003